

SOX10

Human Disease Association

WS4–Waardenburg syndrome type 4, also known as Waardenburg Shah syndrome, is characterized by hypopigmentation of skin and hair, deafness, and megacolon resulting from intestinal aganglionosis (Hirschsprung disease). Numerous *SOX10* mutations have been associated with this disorder ([Bondurand et al., 1998](#)) as well as *SOX10* deletions ([Bondurand et al., 2007](#)). WS4 is also associated with mutations in *EDNRB* and *EDN3*.

PCWH–Peripheral demyelinating neuropathy, Central dysmyelinating leukodystrophy, Waardenburg syndrome, and Hirschsprung disease exhibits WS4 phenotypes with additional peripheral nervous system defects, and results from mutations in *SOX10*. Most WS4- and PCWH-associated alleles of *SOX10* contain mutations that result in premature termination codons and generate truncated protein. PCWH mutations are found in the C-terminal transactivation domain of *SOX10*, while most of the WS4-associated *SOX10* mutations are seen either near the N-terminus or near the HMG-domain ([Inoue et al., 2002](#)). While all mutations of *SOX10* that result in truncated protein generate a protein with a dominant negative effect in vitro, mutant alleles associated with PCWH allow the mutant mRNAs to escape the nonsense-mediated decay pathway, resulting in a mutant protein with a dominant negative function, while WS4 mutant alleles do not escape nonsense-mediated decay and are thus degraded rapidly ([Inoue et al., 2004](#)). Conflicting with this hypothesis, however, two PCWH patients were found to harbor a deletion encompassing the entire *SOX10* locus (of note, one of these patients harbored an apparently irrelevant missense mutation in the intact *SOX10* locus, as measured by in vitro assays) ([Bondurand et al., 2007](#)). One PCWH-associated *SOX10* mutation, 1400del12, is a deletion that leaves the *SOX10* protein sequence intact but results in translation of 82 novel amino acids at the C-terminus. This allele does not confer a dominant negative function; instead the novel C-terminal domain disrupts protein function by an undetermined, toxic function ([Inoue et al., 2007](#)).

WS2–Waardenburg syndrome type 2 is characterized by pigmentation abnormalities and deafness, but does not display the additional phenotypes seen with other WS types. Analysis of genetically unexplained WS2 patients found that some WS2 patients harbor deletions of *SOX10*, and the frequency of these WS2 *SOX10* mutations was similar to the frequency of WS2 *MITF* mutations, suggesting *SOX10* is a major WS2 gene. Two of these WS2 patients with *SOX10* mutations also displayed peripheral neuropathy similar to that of PCWH, indicating that the molecular alterations that cause the clinically defined WS subtypes are overlapping ([Bondurand et al., 2007](#)). Three additional WS2-associated *SOX10* mutations were discovered in Chinese patients, at a frequency similar to that of *MITF* mutations, lending further support to the hypothesis that *SOX10* is a major contributor to the pathogenesis of WS2 ([Chen et al., 2010](#)).

Yemenite deaf-blind hypopigmentation syndrome (YDBS)–This rare disorder is characterized by ocular defects, deafness, and pigmentation abnormalities. Three patients, two of whom were siblings, have been reported with YDBS. The siblings with more severe phenotypes did not show a *SOX10* mutation, while the 3rd patient with a milder form of the disease harbored a *SOX10* missense mutation. This patient showed hypo- and hyperpigmentation of the skin, gray hair, white eyelashes and eyebrows (but normal vision), and hearing loss ([Bondurand et al., 1999](#)). This YDBS-associated *SOX10* missense mutation was located within the DNA-binding domain, and prevents SOX10 function on the *MITF* promoter but still allows SOX10 to complex with PAX3 to activate the *c-RET* promoter, which functions in enteric ganglia development, thus explaining the absence of enteric ganglia defects in YDBS ([Lang and Epstein, 2003](#)).

Charcot-Marie-Tooth disease–This disease describes a group of progressive, chronic peripheral neuropathies. A mutation in the promoter region of the peripheral myelin protein Connexin 32 is associated with this disease, and this mutation specifically affects the ability of SOX10 to activate its transcription ([Bondurand et al., 2001](#)).

HSCR– Hirschsprung disease, also known as aganglionic megacolon, is associated with the absence of ganglia in the distal gastrointestinal tract. Screening of 196 isolated HSCR cases identified a two nucleotide deletion in *SOX10* encoding a frameshift, addition of 56 novel amino acids, and a premature stop codon (c.153-155del; G52Afs108X). This represents the first association of a *SOX10* mutation with HSCR alone (Sanchez-Mejias et al., 2010).

Overexpression of *Sox10* using transgenic mice with targeted *Sox10* expression to developing gonads resulted in XX sex reversal in mice, showing that SOX10 functions in gonadal development, and may be responsible for rare human disorders of sexual development that are associated with human chromosome 22q (Polanco et al., 2010).